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NOTE.—Numerous references to earlier articles by these same authors and by other authors will be found in the papers cited above.

## THE ABSENCE OF PANCREATIC SECRETIONS IN SPRUE AND THE EMPLOYMENT OF PANCREATIC EXTRACT IN THE TREATMENT OF THIS DISEASE.

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Our ideas of sprue as a clinical entity date from the works of Manson, Vander Burg and Fayrer in the '80s, although it has been recognized since 1737, and Hillary clearly defined it in 1766. Manson described it as a disease of the tropics, characterized by "a peculiarly inflamed, superficially ulcerated, exceedingly sensitive

condition of the tongue and mouth; great wasting and anemia; pale, copious and often loose, frequent and frothy, fermenting stools; very generally by more or less diarrhea, and also by a marked tendency to relapse." Castellani and Chalmers, in the last edition of their *Manual of Tropical Medicine*, 1919, define it as follows: "Sprue is a chronic catarrhal inflammation of the alimentary canal of unknown cause, characterized by a peculiar ulcerative condition of the tongue and mouth and by the passage of large, pale, smooth motions, the symptoms waxing and waning periodically." The disease is endemic in certain parts of Asia, affecting primarily the Europeans, though the natives are not immune, and it is widely distributed all through the tropics (under various names, such as Ceylon sore-mouth, psilosis, diarrhea alba, aphthæ tropicæ, etc.), while ever increasing communication between tropical and temperate countries has resulted in more and more cases being seen in Europe and in North America. Recently renewed interest has been aroused in the United States of America in the subject of sprue by the work of Wood, who calls attention to the fact that a certain number of cases regarded as atypical pellagra, and seen in our Southern States, are in reality mild but definite cases of sprue. Unquestionably, living in hot, humid climates, previous wasting diseases and improper diet render one more susceptible to the disease, but the definite etiologic factor or factors have not as yet been absolutely determined, although, at the present writing many authorities, probably the majority, are in favor of regarding the disease as due to a monilium infection. Kohlbrugge's theory that the disease is due to infection by Monilium or Oidium albicans has been supported by Bahr and others, though Castellani has described several other varieties of monilium in the stools of patients with sprue, while Ashford believes that it is not Monilium albicans but another parasite—Monilium psilosis—that is the cause of the infection, and he and others believe that they have definitely proved this by immunologic and vaccine studies, by agglutination and complement-fixation tests and by feeding experiments on monkeys with reproduction of the disease. Dold and others, however, believe that "an excessive acid- and gas-producing microbe is an essential factor in the disease," and "that in various countries different kinds of organisms having the same pathologic effects will be found causing this disturbance." In this connection it may be mentioned that Castellani has reported a number of cases markedly improved by the administration of large doses of bicarbonate of soda, while certain writers believe that the disease is produced by certain cocci or protozoa. Unquestionably the two theories most supported are either that the disease is in reality a moniliasis, due to one or several varieties of this fungus or that it is due to dietetic errors and probably represents a real deficiency disease, as McCarrison has especially suggested.

As one would expect from the symptoms, most authorities lay special stress upon the *pathologic anatomy* of the disease as it affects the *digestive tract*, although Manson has insisted that while certain of the findings undoubtedly represent the *primary* lesions due to the disease, others unquestionably represent the effect of the *secondary* long-lasting tissue starvation due to the disease and are very similar in character to the intestinal findings in famine patients. Certainly in all severe, chronic cases there is "an irreparable destruction of the mucous membrane of the alimentary canal both of the secreting and absorbing tissues" (Manson), all leading to the thinned intestine with diaphanous wall, with absence or marked diminution of villi and glands, congestion, ulceration and erosion, and sometimes cicatricial replacement, which are obviously basic causes of the digestive symptoms which dominate the picture and which are due to the effect of such a pathologic condition upon the digestion and assimilation. Microscopically we meet with small-cell infiltration, a smooth and atrophic mucous membrane, small follicular ulcers, notably in the lower ileum, the primary lesions, according to Castellani, being beneath the epithelium in both the tongue and intestine, the former producing the peculiar mouth picture so characteristic of the disease.

Certainly, whatever the primary causes, digestion and absorption are very markedly affected by the pathologic conditions produced, and the acids produced in such abundance must markedly disturb digestion, notably the emulsification and digestion of the fats, so that there is often 40 to 50 per cent. of undigested fat in the stools. Certain authorities believe also that the changes that have been described in the liver leading finally to atrophy lessen so markedly the detoxifying properties of this organ as to add a definite picture of intestinal toxemia to the other symptoms of the disease.

Strange to say, after a very careful searching of the literature we have been unable to find in detail any careful notes as to the microscopic changes in the *pancreas* in sprue: most authors, such as Manson and Schmidt, do not mention it at all in their description of the pathology of the disease; others content themselves with stating that the pancreas is normal, inflamed or cirrhotic, this probably based on macroscopic findings, as no note is made of the microscopic examination of this organ.

In 1916 we published[1] the results of our quantitative studies of the pancreatic ferments in a case of sprue sent to us from Porto Rico, and finding that all three ferments—trypsin, lipase and diastase—were absent, administered pancreatin to the patient in addition, of course, to the recognized treatment of this disease, and were very much struck with the remarkable improvement that took place, an improvement coincident with the administration of

[1] Johns Hopkins Hosp. Bull., October, 1916, No. 308.

pancreatic extract and stopping with a recurrence of the symptoms shortly after the pancreatic extract was withdrawn, so that for the patient to remain perfectly well clinically it was essential to administer the extract constantly. While many had suggested that there was a diminution or absence of pancreatic ferments, as obviously suggested by the character of the stools, notably the large excess of undigested fat therein, we believe that ours was the first case in which this was definitely proved by very careful and repeated estimations of these ferments.

Since our first case we have had the opportunity of studying 4 other cases—thus making 5 in all—2 coming to us from Porto Rico and 3 from the Philippines. All had been diagnosed as sprue by experts in this disease and were of long duration, and in none had the symptoms been present for less than one year. In each case the symptoms were typical: gradual onset, sore-mouth, diarrhea very marked in the morning, indigestion, increasing loss of weight, diminished appetite in 4 of the cases, abdominal discomfort, much gas, a marked tendency to ballooning of the abdomen, which in one of the cases was of the maximum degree, often coming on with no apparent cause and producing great discomfort; the tendency to relapse had been noted in each of the cases. The stools were characteristically frequent, voluminous, frothy, gray in 4 cases, yellow in one, with mucus, many bacteria, acid reaction and marked excess of fat; we did not, however, make very careful studies of the stools for monilium or other intestinal parasites. By proper methods bile pigments could be demonstrated in the stool in every case, and the gray color, therefore, was not due to lack of bile but was probably caused by lenkourobilin—a not at all improbable transformation in the absence of pancreatic secretions—although Castellani believes that in certain cases this color is due to various bacteria, as, for instance, Bacillus alhafaciens.

Our *quantitative* estimation of the pancreatic ferments was made from studies of the stool in all our cases and from the duodenal contents obtained with the Einhorn bucket in 3 cases. These quantitative estimations of the ferments in the stool were made once in 1 case, twice in 3 cases and five times in 1 case, there being an interval of nearly a year between the third and fourth and fourth and fifth estimations. The methods employed were those previously described by us;[2] for the diastase we used a modification of the Wohlgemuth method, for the trypsin the Fuld casein method, for the lipase 1 per cent. monobutyrin, while the same methods, with slight modifications in regard to dilution, were used in estimating the ferments in the duodenal contents. In both our 5 cases, both in the original experiments and in the repetitions of the tests, whether with the stool, which we regard as more exact quantitatively, or

[2] Johns Hopkins Hosp. Bull., September, 1912, No. 259; July, 1914, No. 281 and elsewhere.

with the duodenal contents, none of the pancreatic ferments was found, or in such minimal amounts as to fall within the limits of error. Thus in the case of diastase we had previoosly estimated the low normal amount of this ferment in the stool after the method which we had described and which was based on the study of a large number of normal cases.[3] This low normal amount we found to be 600 starch gram units, but in each of our cases of sprue the reading showed less than 12 units, this being our tube of greatest dilution, as we regard it as impossible to draw any conclusions as to lesser amounts than this. All these findings are so striking that we feel that it is beyond question that certain of the chronic cases of sprue are associated with a complete absence of pancreatic secretion, and this must play a role in the prodoction of the symptoms, although, of course, our series is far too small to deduce from it any general conclusions. We should have liked to have estimated qoantitatively the intestinal ferments in these cases as well, but the inherent difficulties are so great and the readings obtained so open to criticism that this procedore was not carried out. Nevertheless, if one can judge from the pathologic findings there must be an enormous diminution in the intestinal ferments, and the effect of the absence or diminution of certain of these, such as erepsin, enterokinase, the inverting ferments, possibly the duodenal hormone which brings about pancreatic secretion, and, at the same time, the disturbances in the chemistry of the chyme, notably as regards reaction and character of the bile, must play an enormous role, not only *per se*, but in the effect of these variations from the normal upon the secretion of the pancreatic juice. Whether this absence represents organic changes in the gland, whether it is due to functional disturbance or to destruction or changes due to lack of activation of the ferments after they have reached the duodenum, are obviously questions which we are unable to answer. In regard to the gastric contents of our 5 cases, 1 showed hyperacidity, 2 subacidity, 2 achlorhydria, but in the case of these last two groups a return to a practically normal gastric contents was coincident with the very marked clinical improvement noted; the one case that showed no improvement under treatment was that associated with hyperchlorhydria. Both the cases with achlorhydria showed a return of acid very shortly after they began to show improvement in symptoms. Castellani has noted that the test-meal may show diminished hydrochloric acid and pepsin, while Van der Scheer found no special changes in either gastric secretion or gastric motility in his 13 cases. Certainly, in oor small experience the gastric picture is neither constant nor significant.

In regard to *treatment*, the usual therapeutic measures in vogue—encouragement, absolute rest, fresh air, sunshine and a very carefully selected diet—were used in all cases. As regards diet, in the 4 of

[3] Johns Hopkins Hosp. Bull., July, 1914, No. 281.

our cases that did so well n diet beginning with buttermilk, which we chose in place of ordinary milk because these cases showed deficiency of acid in the gastric juice, then gradually adding egg, zwieback, bread-and-milk and other simple, soft and liquid foods, including fruit juice and purée of fruits, was so well borne that there was no need of trying other special diets. All these cases had obviously tried change of climate but none had been given monilia vaccines. In the fifth case—the one that showed no improvement whatsoever on this diet— we tried fruit diet and meat diet, with special attention to strawberries in the former, but neither was well borne; in fact, all diets seemed to be equally poorly borne, and the only means of helping him seemed to be courses of neosalvarsan intravenously, and this produced a marked temporary improvement, as it had done previously in his case in the Philippines. In the cases with subacidity or anacidity we gave hydrochloric acid until their gastric contents gave practically normal figures. In the case with excessive hydrochloric acid we used sodium bicarbonate in large amount, but, if anything, this seemed to add to his distention and his discomfort. We did not try yellow santonin, so strongly recommended by Begg, nor did we think appendicostomy and irrigation, as suggested by Van der Scheer, advisable or justifiable.

In all of our cases, based on our finding of the complete absence of pancreatic secretion, we gave large doses of pancreatin or some form of pancreatic extract, 5 to 10 grains, with 20 to 40 grains of calcium carbonate or calcium lactate three times daily, two hours after the larger feedings; in 4 of the cases the results were really so remarkable, the treatment seemed so markedly efficacious and the improvement so rapid as to make each one feel that it was definitely due to their being supplied with the ferments in which they were deficient. This improvement persisted as long as the treatment continued; 3 of the 4 cases were lost sight of in three or four months after the treatment started, but they seemed clinically much better. The fourth case—a patient who had moved from Porto Rico to Virginia and was constantly near enough to be seen every few months—continued well so long as she took the pancreatin; in fact, while on the treatment she was clinically absolutely free of all signs and symptoms of the disease and looked and seemed absolutely well. On the other hand, if she stops the pancreatin for a few days the tongue becomes sensitive and sometimes red, she developed a morning diarrhea and the abdomen feels distended and uncomfortable, and the stool becomes more voluminous and unquestionably shows increasing fermentation. But all these symptoms rapidly disappear with the readministration of the ferment. This case has been carefully studied n number of times in the years that she has been under our observation, but the stool still always shows a complete absence of secretion from the pancreas, and it is quite obvious that, in her case at least, health is absolutely dependent upon the regular and

constant administration of pancreatin. The fifth case showed absolutely no benefit from the use of pancreatin; his was the longest history—over three years—although on admission he apparently was by no means so ill as our first case—the one who has been studied the most carefully of our series, though he was definitely more ill clinically than the other three. We have felt in his case that the destruction of glandular tissue was so great that there must have been such reduction in intestinal ferments, in addition to his complete pancreatic insufficiency, that he was unable to either digest or assimilate more than the very minimum amount of food, and, in this case, we should have liked to have tried intestinal ferments and possibly liver extract in addition to what we were giving—whether they would have produced any benefit is obviously problematical.

These cases are far too few in number to justify us in drawing definite general conclusions in regard to the pancreatic secretions in sprue, but we do feel that they add something to our knowledge of the secretory disturbances met with in this disease and are worth recording, both from the point of view of pathology and of treatment. The careful study of these cases leads one to certain queries anent this disease: Is sprue one or several diseases? Are the major portion of the symptoms due to the primary lesion or are many of them much better explained on the basis of secondary starvation? Is it possible to explain the picture on the assumption that it represents an infection due to a monilinia and, if so, is one or several species involved? Or may various organisms or groups of organisms having the common quality of producing marked acid fermentative changes in the chyme bring about these symptoms? What role does diet play? May this possibly be a new member of the ever-increasing group of deficiency diseases? Is sprue very much more widely disseminated in temperate climates than has hitherto been supposed and may it play some role in certain of the vague chronic digestive disturbances so frequently met with in countries which lie in the southern portions of our temperate zones, for example, our southern states.

Whatever our answer be to these queries, we do feel that the study of our cases shows that in certain at least of the chronic cases of the disease (1) there is a practically complete absence of the pancreatic ferments, and (2) that while, obviously, all the well-recognized forms of treatment—dietetic, hygienic, etc.—should be rigorously carried out, nevertheless very great improvement and, in some cases, apparently clinical cure can be brought about by regular and constant administration of pancreatin.